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#13

PATENT
ATTORNEY DOCKET NO: 04843/080001

## COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am an original, first and joint inventor of the subject matter which is claimed and for which a patent is sought on the invention entitled CELL IMPLANTATION THERAPY FOR NEUROLOGICAL DISEASES OR DISORDERS, the specification of which

- ☐ is attached hereto.
- ■ was filed on July 27, 2000 as Application Serial No. 09/626,677.
- ☐ was described and claimed in PCT International Application No. _____ filed on _____ and as amended under PCT Articie 19 on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose all information I know to be material to patentability in accordance with Title 37, Code of Federal Regulations, § 1.56.

**NON-PROVISIONAL PRIORITY RIGHTS**: I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose all information I know to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

| Serial Number | Filing Date | Status |
|---|---|---|
| 09/626,677 | July 27, 2000 | Pending |

I hereby appoint the following attorneys and/or agents to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Paul T. Clark, Reg. No. 30,162, Karen L. Elbing, Ph.D. Reg. No. 35,238, Kristina Bieker-Brady, Ph.D. Reg. No. 39,109, Susan M. Michaud, Ph.D. Reg. No. 42,885, James D. DeCamp, Ph.D., Reg. No. 43,580, Sean J. Edman, Reg. No. 42,506.

Address all telephone calls to: Paul T. Clark at 617/428-0200.

Address all correspondence to: Paul T. Clark at Clark & Elbing LLP, ~~476~~ 101 Federal Street, Boston, MA 02110. **Customer No: 21559**

## COMBINED DECLARATION AND POWER OF ATTORNEY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

| Full Name (First, Middle, Last) | Residence Address (City, State, Country) | Post Office Address (Street, City, State, Country) | Citizenship |
|---|---|---|---|
| Ole Isacson | Cambridge, Massachusetts | 14 Ellery Square Cambridge, MA | ~~Swedish~~ U.S.A. |
| Signature: | | | Date: 7/11/02 |

| Full Name (First, Middle, Last) | Residence Address (City, State, Country) | Post Office Address (Street, City, State, Country) | Citizenship |
|---|---|---|---|
| Kwang Soo Kim | Lexington, Massachusetts | 27 Lillian Road Lexington, MA | Korea |
| Signature: | | | Date: 7/11/02 |

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#13 Declaration w/ att.

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Certificate of Mailing: Date of Deposit: Dec. 2, 2002

I hereby certify under 37 C.F.R. § 1.8(a) that this correspondence is being deposited with the United States Postal Service as **first class mail** with sufficient postage on the date indicated above and is addressed to: BOX RCE, Commissioner for Patents, Washington, D.C. 20231.

Julie A. Bowen
Printed name of person mailing correspondence

Julie A. Bowen
Signature of person mailing correspondence

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

| | | | |
|---|---|---|---|
| Applicant: | Ole Isacson *et al.* | Art Unit: | 1632 |
| Serial No.: | 09/626,677 | Examiner: | A. Baker |
| Filed: | July 27, 2000 | Customer No.: | 21559 |
| Title: | CELL IMPLANTATION THERAPY FOR NEURODEGENERATIVE DISEASE OR DISORDERS | | |

BOX RCE
Commissioner for Patents
Washington, D.C. 20231

## DECLARATION OF OLE ISACSON UNDER 37 C.F.R. § 1.132 TRAVERSING GROUNDS OF REJECTION

Under 37 C.F.R. § 1.132 and regarding the rejection of claims 1-11 under 35 U.S.C. § 112, first paragraph, for lack of enablement. I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application.

2. I received a doctorate degree in neurobiology and a medical degree from the University of Lund. I have worked in the fields of neurobiology and neurology for over 20 years and have published over 200 primary research articles, review articles, and

invited book chapters. My academic appointments have included a Fellowship in Neurobiology at the University of Cambridge (England) and academic professorships at the Harvard Medical School and Massachusetts General Hospital. Presently, I am the Director of both the Neuroregeneration Laboratories and The Udall Parkinson's Disease Research Center of Excellence, at the McLean Hospital.

My curriculum vitae and publication list is attached (Exhibit A).

3. Parkinson's Disease (PD) is a neurodegenerative disorder characterized by a progressive loss of midbrain dopaminergic (DA) neurons. Cell replacement therapy has been successfully used to treat PD. This strategy is, however, limited by the availability of cells capable of replacing the lost dopaminergic neurons and their synapses. The claimed invention is a cell replacement therapy for PD that transplants embryonic stem (ES) cells that have been lineage-restricted to dopaminergic neurons.

4. As shown in the attached publication from my laboratory (Chung *et al.*, Eur. J. Neurosci., 16:1829-1838, 2002; Exhibit B), which used the methods described in the present specification, ES cells that express exogenous Nurr-1 *in vitro* adopt a dopaminergic phenotype. Specifically, a mouse blastocyst-derived ES cell line was stably transfected with a vector expressing Nurr-1 under the control of the elongation factor-1α promoter and grown in the presence of leukemia inhibitory factor (LIF) and, optionally, Shh and FGF-8. ES cell lines successfully transfected with Nurr-1 expressed high levels of dopaminergic markers including, for example, tyrosine hydroxylase (TH), L-amino acid decarboxylase (AADC), and the dopamine transporter (DAT). These results were confirmed using both immunocytochemistry and RT-PCR (see Figures 2-4). The Nurr-1-expressing ES cells also adopted functional characteristics of DA neurons. Figure 7 demonstrates that Nurr-1 expression resulted in a significantly high level of dopamine secretion compared to control ES cells.

5. ES cells that express exogenous PTX-3 *in vitro* adopt a dopaminergic phenotype. Our laboratory has also created mouse blastocyst-derived ES cell line that expresses PTX-3. Figure 1 of Exhibit C demonstrates the successful expression of PTX-3 in D3 ES cells. The PTX-3-expressing ES cell lines were cultured and analyzed in an identical manner as described for the Nurr-1-expressing ES cell lines. Figure 2 of Exhibit C demonstrates that ES cells expressing PTX-3 (P2 and P5) also adopt a specific and desirable dopaminergic phenotype. Specifically, we measured a significant increase in TH, dopamine decarboxylase (DDC), and aldehyde dehydrogenase-2 (AHD2). Although the expression pattern of dopaminergic markers was slightly different from the Nurr-1-expressing ES cells (N2), the PTX-3-expressing ES cells have definitely adopted the dopaminergic phenotype that selectively dies or degenerates in Parkinson's Disease.

6. The Examiner has also questioned whether these modified ES cells can be successfully transplanted in the brain. Although similar work is ongoing in my laboratory, I direct the Examiner's attention to a recent publication by Dr. Ron McKay at the National Institute of Health (Kim *et al.*, *Nature* advance online publication, 20 June 2002; Exhibit D). Here, Dr. McKay and his colleagues create rat midbrain CNS precursors by expressing Nurr-1 in ES cells and culturing them in the presence of Shh and FGF-8 (see Figure 2). These ES cells are equivalent to the cells of the present invention which are lineage-restricted to DA neurons. Dr. McKay engrafted these lineage-restricted ES cells into the brains of hemiparkinsonian rats, lesioned using 6-hydroxydopamine. Dr. McKay demonstrate that these ES cells not only integrate and survive in the adult rat brain (Figure 3), but they are capable of partially reversing the motoric deficits caused by the experimental ablation of the DA neurons (Figure 5).

The transplantation techniques used by Dr. McKay were standard techniques available to the artisan at the time of filing of the present application. Thus, the

experimental results presented in Exhibit D provide a working example of the presently claimed method. All of the reagents and techniques used in Exhibit D were either known in the art at the time of application filing, or were provided in the present specification.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

December 2nd 2002

Date

Ole Isacson, M.D., Ph.D.